

### Remarks

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested. Support for the phrase “differentiate into O4 positive oligodendrocytes, when cultured in PDGF, FGF2, and NT3, and further develop into galactocerebroside positive oligodendrocytes in the presence of 5% PBS/IGF-1” is found in Figure 4 of the present application. Support for the above amendments to claims 42-45 is found on page 21, lines 24-28 of the present application. No new matter is added.

The rejection of claims 42-45 under 35 U.S.C. § 112 (1<sup>st</sup> para.) for failure to satisfy the written description requirement is respectfully traversed in view of the above amendments.

The rejection of claims 42-45 under 35 U.S.C. § 102 or 35 U.S.C. § 103 as anticipated by or for obviousness over U.S. Patent No. 6,361,996 to Rao, et. al., (“’996 patent”) is respectfully traversed.

The ’996 patent discloses multipotential neuroepithelial stem cells and lineage-restricted astrocyte/oligodendrocyte precursor cells (the ’996 patent Abstract). The astrocyte/oligodendrocyte precursor cells are derived from the neuroepithelial stem cells, are capable of self-renewal, and can differentiate into astrocytes and oligodendrocytes but not neurons (*Id.*). Figure 1 of the ’996 patent and the supporting text of the specification refer to cell type 14 as a multipotential precursor cell that can generate oligodendrocytes 18 and astrocytes 22. Cell type 14 is said to be generated from embryonic spinal cord stem cells. Figure 2 of the ’996 patent depicts multipotent neuroepithelial stem cells 50 which differentiate into oligodendrocyte-astrocyte progenitor cells 54 that are capable of self-renewal as well as further differentiating into oligodendrocytes 58, type 1 astrocytes 62, and type 2 astrocytes 66 (col. 17, lines 4-9). The ’996 patent characterizes these cells as “multipotential intermediate precursor cells restricted to glial lineages” (emphasis added) (the ’996 patent col. 23, lines 1-5). Examples 14 and 15 of the ’996 patent demonstrate that the astrocyte/oligodendrocyte precursor cells have strong bias to differentiate to astrocytes. In particular, Example 14, at col. 20, lines 44-60, states:

After 5 days of culturing, NEP cells in the absence of CEE, cells were immunopurified, plated on fibronectin/laminin coated dishes, and exposed to cytokines previously associated with differentiation of precursor into

oligodendrocytes, astrocytes, or neurons. The A2B5-panned population was >98% positive of A2B5<sup>+</sup> cells when stained one hour after panning. Staining 24 hours after plating showed that all cells of the panned population were A2B5<sup>+</sup> and did not express any other lineage markers tested.

Panned cultures in the presence of bFGF and no other growth factors for 5 days consisted of 1% oligodendrocytes, 50% GFAP<sup>+</sup> astrocytes, and 49% A2B5<sup>+</sup> cells. The proportion of differentiated cells was significantly shifted when the bFGF-containing medium was replaced after 3 days with medium supplemented only with PDGF. Under these conditions, the culture consisted of 30% oligodendrocytes, 50% astrocytes, and 20% A2B5<sup>+</sup> cells.

Similarly, Example 15 of the '996 patent (col. 21, line 59 to col. 22, line 11) states that as a result of culturing in CNTF and bFGF, the A2B5<sup>+</sup> cells predominantly differentiate into cells with a type-2 astrocyte phenotype. This is entirely consistent with the previously submitted Second Declaration of Mahendra S. Rao, M.D., Ph.D. Under 37 C.F.R. § 1.132 ("Second Rao Declaration"). Gregori et al., "The Tripotential Glial-Restricted Precursor (GRP) Cell and Glial Development In the Spinal Cord: Generation of Bipotential Oligodendrocyte-Type-2 Astrocyte Progenitor Cells and Dorsal-Ventral Differences In GRP Cell Function," *J. Neurosci.* 22(1):248-256 (2002) has suggested that the '996 patent describes a glial progenitor that gives rise to a more restricted astrocyte/oligodendrocyte precursor that still directly makes predominantly astrocytes and a small minority of oligodendrocytes (Second Rao Declaration ¶ 7). Thus, cells in the '996 patent's pathway to oligodendrocyte production are bi-potential astrocyte/oligodendrocyte progenitor cells that have strong astrocytic bias (*Id.*). This bias of the '996 patent's astrocyte/oligodendrocyte progenitor to differentiate to astrocytes clearly distinguishes them from the presently claimed oligodendrocyte progenitor cells, the majority of which mature into oligodendrocytes. This is particularly true with respect to new claims 42-45, which require that  $66.3 \pm 6.8\%$  of cells in the enriched or purified preparation mature into O4-IR oligodendrocytes when cultured in the presence of 5% FBS/IGF-1.

It is important to note that multiple pathways to generate post-mitotic, mature oligodendrocytes, have been described (*Id.*). Anderson and colleagues have shown that an oligodendrocyte/motor neuron precursor exists that does not make astrocytes (Zhou et al.,

"The bHLH Transcription Factors OLIG2 and OLIG1 Couple Neuronal and Glial Subtype Specification," *Cell* 109:61-73 (2002))(*Id.*). Other investigators have shown distinct sites of origin of oligodendrocytes and astrocytes presumably from separate precursors (Vallstedt et al., "Multiple Dorsoventral Origins of Oligodendrocyte Generation In the Spinal Cord and Hindbrain," *Neuron* 45:55-67 (2005) and Cai et al., "Generation of Oligodendrocyte Precursor Cells from Mouse Dorsal Spinal Cord Independent of *Nkx6* Regulation and *Shh* Signaling," *Neuron* 45:41-53 (2005))(*Id.*). Yet other investigators have shown that different kinds of oligodendrocyte progenitors exist (Pringle et al., "*Egfr3* Expression by Astrocytes and Their Precursors: Evidence that Astrocytes and Oligodendrocytes Originate In Distinct Neuroepithelial Domains," *Development* 130:93-102 (2003))(*Id.*). Since the state of the art suggests that different oligodendrocyte-astrocyte cell profiles exist in different circumstances, there is no reason to believe, as the U.S. Patent and Trademark Office (PTO"), has suggested, that the '996 patent inherently produces another precursor which has the claimed characteristics -- an enriched or purified preparation human mitotic oligodendrocyte progenitor cells, where the majority of cells in the enriched or purified preparation differentiate into O4 positive oligodendrocytes.

The outstanding office action states that the claims are anticipated by Examples 7 and 15 of the '996 patent. According to the PTO, these examples must produce an intermediate between the '996 patent's oligodendrocyte-astrocyte precursor cells and fully differentiated cells. The PTO particularly relies on Example 7's mention of cells that appeared to have a different morphology than the oligodendrocyte type-2 astrocyte progenitors or mature oligodendrocytes in asserting anticipation. Applicants disagree.

Firstly, these examples involve work with rat -- not human -- cells. The PTO responds that one of skill in the art would be motivated to isolate a cell population from humans which is like that recovered by Rao from rats. However, no where does Rao recover the claimed cell population (where a majority of the population differentiate into O4 positive oligodendrocytes) from rats, let alone humans. The PTO asserts that those skilled in the art would have the desire to find such human oligodendrocyte progenitor cells. However, even with such a desire, there is no reason to believe that it is achievable where Rao does not teach the claimed cells in rats or humans. In view of Rao's failure to produce rat cells where a majority of those cells differentiate into O4 positive oligodendrocytes, there can be no expectation of success in producing human cells with that capability.

Secondly, the mention of cells having a flattened morphology that is different than the oligodendrocyte type-2 astrocyte progenitors or mature oligodendrocytes does not mean

that those additional cells are the claimed oligodendrocyte progenitor cells. The PTO's point is entirely speculative and is contrary to what Dr. Rao said in his second declaration. In taking this position, the PTO is impermissibly ignoring the testimony of Dr. Rao who is in a far better position to know what cell types his work made and did not make. The fact that mature oligodendrocytes were present does not support the PTO's position. There is no evidence to suggest that these are progenitor cells; to the contrary, they do not have the typical morphology that would be expected of oligodendrocyte progenitors under these culture conditions. One of ordinary skill in the art would have expected that the oligodendrocyte type-2 astrocyte progenitors, having an astrocyte bias, would differentiate into astrocytes. Even if there was an intermediate between Rao's oligodendrocyte type 2-astrocyte progenitors and mature astrocytes, such intermediate cells would similarly differentiate to astrocytes unlike the oligodendrocyte progenitors of the present invention.

Applicants maintain that claim 26 is patentable of its own accord, because the claimed adult human oligodendrocyte progenitor cells are distinguishable from the '996 patent's glial progenitor cells from newborn rat brain. The PTO's suggestion that this difference in age is not a proper basis for distinguishing the claimed invention is unsupported and completely incorrect. Those skilled in the art would readily recognize that the difference in lineage between the '996 patent's newborn rat cells and the adult human cells of claim 26 constitutes a clear distinction in the cells' stage of development. Simply put, oligodendrocyte progenitor cells from adults and newborns are not the same. See Windrem et al., "Fetal and Adult Human Oligodendrocyte Progenitor Cell Isolates Myelinate the Congenitally Dysmyelinated Brain," *Nature Medicine* 10(1):93-97 (2004) (attached hereto as Exhibit 1). In view of this significant difference, the '996 patent cannot be said to teach or suggest the cells of claim 26.

In the outstanding office action, the PTO asserts that applicants' arguments with regard to Examples 14 and 15 of Rao are irrelevant to the claimed invention to the extent that the claims call for the majority of claimed oligodendrocyte progenitor cells to mature to oligodendrocytes. However, in view of the above amendments, which make clear that a majority of cells in the enriched or purified preparation differentiate into O4 positive oligodendrocytes, this position can no longer be maintained.

The outstanding office action further contends that even if the claims call for a majority of the cells in the enriched or purified preparation to mature into oligodendrocytes, they do not distinguish Rao. Given Rao's clear teaching that his oligodendrocyte-astrocyte precursor cells have an astrocytic bias, it is not apparent how these cells can be regarded as the same as the claimed enriched or purified preparation from which a majority of the cells differentiate into O4 positive oligodendrocytes. In any event, the claims have been amended

to recite the conditions under which a majority of the cells in the enriched or purified preparation can mature into oligodendrocytes (i.e. cultured in PDGF, FGF2, and NT3 and then in the presence of 5% FBS/IGF-1). Since neither of these conditions, let alone the result that a majority of the cells of the enriched or purified preparation differentiate into O4 positive oligodendrocytes are taught by Rao, this reference can hardly be said to teach or render obvious the claimed invention.

Accordingly, the rejection under 35 U.S.C. §§ 102 and 103 is improper and should be withdrawn.

In view of all of the foregoing, applicants submit that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

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